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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,382	03/14/2001	Benjamin Eithan Reubinoff	14418	1139

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/808,382	REUBINOFF ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39,44,45,51,56,57,60,61,67,94,101,105 and 107-115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *108* is/are allowed.

6)☒ Claim(s) *39,44,45,51,56,57,60,61,67,94,101,105,107 and 109-115* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/3/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Remarks, filed 3/19/08 have been considered and entered. Claims 39, 51, 56, 60, 61, 67, 105, 108 are amended; claim 86 is cancelled; claims 114-115 are newly added; claims 39, 44, 45, 51, 56, 57, 60, 61, 67, 94, 101, 105, 107-115 are pending and under current examination.

This action is non-final.

Information Disclosure Statement

Applicants' IDS, filed 6/3/08, has been considered.

Claim Rejections - 35 USC § 112

The prior rejection of claims 39, 44, 45, 60, 61, 67, 94, 101, 105, 106, 108, 110, 111 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' amendment to the claims, which now recite culturing hES cells on fibroblast feeder cells.

Claim Rejections - 35 USC § 102

The prior rejection of claims 51, 86, 107 and 108 under 35 U.S.C. 102(b) as being anticipated by Brustle (Canadian Patent, CA 2315538, published 7/1/99) is withdrawn in view of Applicants' amendment to the claims which now require culturing undifferentiated pluripotent hES cells for 2-3 weeks on fibroblast feeder cells. The withdrawal of the rejection of claim 108 is in view of Applicants' arguments that Brustle teach culturing neural precursor cells, not undifferentiated, pluripotent hES cells, in a serum free medium.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 39, 44, 45, 51, 60, 67, 94, 101, 109-111, 114 are rejected under 35 U.S.C. 103(a) as being unpatentable Thomson *et al.* (Science, 282: 1145-1147, 1998, of record) in view of Brustle (Science, 285:754-756, 1999, of record). This rejection is reinstated upon further consideration by the Examiner.

The basis of this rejection has been set forth in prior Office actions, and in particular, on pages 5-6 of the Office action mailed 7/29/04. With regard to the limitation that the undifferentiated pluripotent hES cells are cultured for 2-3 weeks on fibroblast feeder cells in order to generate differentiating cells, Thomson teach that when hES cells are grown to confluence and allowed to pile up in the culture dish, the hES cells differentiated spontaneously in the presence of fibroblasts, and that they were allowed to differentiate for 2-3 weeks, various markers were detected in the conditioned culture medium that indicated endoderm and trophoblast differentiation. See p. 1146, col. 1, 2nd ¶. Given that Thomson teach methods in which to differentiate hES cells, such as allowing the cells to spontaneously differentiate on fibroblast feeder cells for 2-3 weeks, it would have been obvious to utilizing Thomson's teaching to modify the methods as taught by Brustle, to use human ES cells, allowing the cells to spontaneously differentiate and then induce cells to neural precursor cells, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification to provide differentiated cells for drug discovery and/or transplantation therapies.

Claims 56, 57, 112 and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* (Science, 282: 1145-1147, 1998, of record) in view

of Brustle (Science, 285:754-756, 1999, of record) as applied to claims 39, 44, 45, 51, 60, 63, 64, 67, 94, 101, 109-111, 114 above, and further in view of Stemple (of record). This rejection is reinstated upon further consideration by the Examiner.

The basis of this rejection has been set forth in prior Office actions, and in particular, on pages 6-7 of the Office action mailed 7/29/04. With regard to the limitation that the undifferentiated pluripotent hES cells are cultured for 2-3 weeks on fibroblast feeder cells in order to generate differentiating cells, Thomson teach that when hES cells are grown to confluence and allowed 1to pile up in the culture dish, the hES cells differentiated spontaneously in the presence of fibroblasts, and that they were allowed to differentiate for 2-3 weeks, various markers were detected in the conditioned culture medium that indicated endoderm and trophoblast differentiation. See p. 1146, col. 1, 2nd ¶. Given that Thomson teach methods in which to differentiate hES cells, such as allowing the cells to spontaneously differentiate on fibroblast feeder cells for 2-3 weeks, it would have been obvious to utilizing Thomson's teaching to modify the methods as taught by Brustle, to use human ES cells, allowing the cells to spontaneously differentiate and then induce cells to neural precursor cells, with a reasonable expectation of success. Additionally, it would have been obvious to the ordinary skilled artisan to culture human ES cells by Thomson in DMEM/F12 media in the presence of FGF2 and EGF on polyornithine to form neural precurors as taught by Brustle, but growing the precursors in media comprising retinoic acid and by growth on poly-D-lysine plates to induce neuronal growth, as taught by Stemple, for producing differentiated cells for drug discovery and/or transplantation therapies.

Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson, Brustle and Stemple, as applied to claims 39, 44, 45, 51, 56, 57, 60, 63, 64, 67, 94, 101, 109-112, 114 and 115 above, and further in view of Ben-Hur *et al.* (of record). This rejection is reinstated upon further consideration by the Examiner.

The basis of this rejection has been set forth in prior Office actions, and in particular, on pages 7-8 of the Office action mailed 7/29/04. The limitation that the pluripotent hES cells are cultured for 2-3 weeks on fibroblast feeder cells in order to generate differentiating cells is addressed above. Accordingly, this rejection is reinstated for reasons of record and those cited above. Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture human ES cells as taught by Thomson in DMEM/F12 media in the presence of FGF2 and PDGF-AA on polyornithine to form glial precursors and then in the absence of the growth factors to form predominantly oligodendrocytes and astrocytes as taught by Brustle but growing the precursors on poly-D-lysine and fibronectin coated plates to enhance the presence of neurons in the differentiated cells and in the presence of EGF to enhance neuron differentiation followed by culture with EGF and T3 to produce a culture of neuronal cells, oligodendrocytes and astrocytes for drug discovery and/or transplantation therapies.

New Grounds of Rejection.

Claims 39, 44, 45, 51, 60, 67, 94, 101, 105, 107, 109-111, 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brustle (Canadian Patent, CA 2315538, published 7/1/99, of record) when taken with Thomson (Science, 282: 1145-1147, 1998, of record).

Brustle teach methods of producing neural precursor cells from human ES cells. See Abstract and p. 8, line 14. They teach the proliferation of ES cells, culturing of the ES cells to a neural precursor stage, proliferation of the neural precursor cell in growth factor-containing serum-free medium, and isolation of the purified precursor cell (see p. 8, lines 23-27), they teach that the serum-free medium contains bFGF and EGF (p. 8, line 35). They teach using these methods with mouse ES cells, they were able to produce neurons (see page 11, line 15, page 12, line 28). They teach that withdrawn of growth factors will induce differentiation *in vitro* and

that immunohistochemical analysis may be done to show the presence for various neuronal cells (pp. 15-16, bridging ¶. They teach culturing undifferentiated neural precursor cells in culture dishes coated with polyornithine and fibronectin to produce neurons. See page 16, lines 23-30). They teach the staining of the cells against antibodies to neuronal markers in order to determine the presence of neurons (see p. 16, lines 30-34).

Note that although Brustle do not explicitly teach all of the specific markers recited in the claims, they show the production of the cells required by the claims, and thus, these cells would necessarily express these markers. See also *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993), which teaches that a reference teaching a claimed process, wherein one of the claimed properties of a product used in the prior art process is inherent but undisclosed by the reference, may be properly applied as art against the claimed process. Additionally, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Brustle do not specifically teach culturing undifferentiated human ES cells for 2-3 weeks on fibroblast feeder cells to produce differentiating cells. However, prior to the time of the claimed invention, Thomson teach that when hES cells are grown to confluence and allowed to pile up in the culture dish, the hES cells differentiated spontaneously in the presence of fibroblasts, and that they were allowed to differentiate for 2-3 weeks, various markers were detected in the conditioned culture medium that indicated endoderm and trophoblast differentiation. See p. 1146, col. 1, 2nd ¶. Given that Thomson teach methods in which to differentiate hES cells, such as allowing the cells to spontaneously differentiate on fibroblast feeder cells for 2-3 weeks, and Brustle further suggest

differentiation of hES cells (using embryoid bodies) it would have been obvious to utilizing Thomson's teaching to modify the methods as taught by Brustle, to use human ES cells, allowing the cells to spontaneously differentiate and then induce cells to neural precursor cells, with a reasonable expectation of success. One of skill in the art would have been motivated to make this modification because the production of differentiating cells from hES cells would be well-within the knowledge of the skilled artisan. The skilled artisan would recognize that differentiating hES cells by either EB formation (such as that taught by Brustle) or by spontaneous differentiation (as taught by Thomson) would yield differentiating cells, which could then be used further in the methods taught by Brustle to produce neuronal cells, which could then be used in drug discovery or transplantation therapies.

Claims 56, 57, 112, 113 and 115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brustle (Canadian Patent, CA 2315538, published 7/1/99) and Thomson (above) as applied to claims 39, 44, 45, 51, 60, 63, 64, 67, 94, 101, 105, 107, 109-111, 114 above, and further in view of Stemple *et al.* (cited previously).

Brustle and Thomson are discussed above. They do not specifically teach using laminin coated plates in a media comprising retinoic acid to grow the neuronal precursor cells. However, Stemple also teaches the growth of the neural stem cells in the presence of retinoic acid (page 983, col. 1, parag. 3, line 11-12). Laminin was known at the time of the instant invention to be an adhesive substrate for neural cell growth and differentiation.

Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture differentiating human ES cells as taught by Thomson, in DMEM/F12 media in the presence of FGF2 and EGF on polyornithine to form neural precursors, as taught by Brustle, by growing the precursors in media comprising retinoic acid and by growth on poly-D-lysine and laminin coated plates

to induce neuronal growth as taught by Stemple for drug discovery and/or transplantation therapies. The cited prior art provides sufficient suggestion, teaching and motivation to reach the claimed invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable Brustle (Canadian Patent, CA 2315538, published 7/1/99), Thomson, and Stemple, as applied to claims 39, 44, 45, 51, 56, 57, 60, 63, 64, 67, 94, 101, 105, 107, 109-115 above, and further in view of Ben-Hur *et al.*

Brustle, Thomson and Stemple are discussed above. Ben-Hur discusses the incubation of neural progenitor cells in the presence of EGF led to the production of astrocytes and oligodendrocytes (p. 3784, figure 7). Ben-Hur also teaches that culture of neural stem cells in the presence of T3 also lead primarily to astrocyte and oligodendrocyte production.

Thus, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture human ES cells, as taught by Thomson, in DMEM/F12 media in the presence of FGF2 and PDGF-AA on polyornithine to form glial precursors and then in the absence of the growth factors to form predominantly oligodendrocytes and astrocytes, as taught by Brustle, but growing the precursors on poly-D-lysine and fibronectin coated plates to enhance the presence of neurons in the differentiated cells and in the presence of EGF to enhance neuron differentiation followed by culture with EGF and T3 to produce a culture of neuronal cells, oligodendrocytes and glia cells for drug discovery and/or transplantation therapies.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Claim 108 is allowed. This claim is free of the prior art of record because it is directed to culturing isolated, undifferentiated hES cells in a serum free medium supplemented with growth factors in order to produce neural progenitor cells. The instant specification teaches that transferring hES cells into serum free media induces differentiation (see ¶ 194 and ¶371 of the published Application). None of the cited art of record recites this step, as the cited art of record is directed to culturing hES cells to produce differentiating cells, which are then cultured in serum-free media.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632